Insulin Sensitivity Measured With the Minimal Model is Higher in Moderately Overweight Women With Predominantly Lower Body Fat

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Lower-body obesity is associated with a lower incidence of diabetes and high values of HDL_2 cholesterol and thus seems to have a metabolic profile opposite to upper-body obesity. We measured insulin sensitivity by the minimal model procedure in 20 lower-body overweight women (age 40.3 ± 2.3 years, waist-to-hip ratio WHR 0.75 ± 0.01, body mass index BMI 29.9 ± 0.7 kg/m^2), compared to 18 women with a similar degree of upper-body obesity (age 40.4 ± 3 years, WHR 0.91 ± 0.02, BMI 29.4 ± 0.7 kg/m^2) and 28 control women matched for age and height. Insulin sensitivity and basal insulin effect were higher in lower-body obesity (11.2 ± 0.2 min^{-1}/[μU/ml] × 10^{-4} and 0.8 ± 0.2 min^{-1} × 10^{-2}, respectively) compared to upper-body obesity (2.6 ± 0.4, $p < 0.001$ and 0.3 ± 0.05, $p < 0.01$) and controls (6.1 ± 0.7, $p < 0.02$ and 0.5 ± 0.07, $p < 0.02$). It is suggested that lower-body obesity could be associated with a reduced free fatty acids-induced inhibition of insulin action by the Randle mechanism. This study confirms that body fat distribution is a more relevant determinant than obesity itself in the pathogenesis of insulin resistance. Contrary to upper-body obesity, moderate lower-body overweight seems to be associated with high values on insulin sensitivity.

■ Key words: Lower-Body Obesity – Insulin Resistance – Minimal Model – Randle Cycle – Cardiovascular Risk

Introduction

Abdominal obesity is associated with an increased risk of cardiovascular disease and related mortality, which seems to be explained, at least in part, by alterations in insulin-glucose homeostasis and blood lipoprotein levels. Insulin resistance has been suggested to be the underlying mechanism of this association between overweight and atherogenetic metabolic abnormalities [1]. However, the lower-body obesity seems to be associated with a lower incidence of diabetes and high values of HDL_2 cholesterol, suggesting a possible protective effect of thigh fat. Thus, lower-body obesity seems to have a metabolic pattern opposite to upper body obesity [2].

We are not aware of studies on insulin sensitivity in this kind of patients. Some reports included massively obese patients in whom the waist-to-hip ratio (WHR) indicated a predominance of lower body fat deposit [3]. They evidenced a strong relationship between increase in WHR and insulin resistance, but insulin sensitivity of subjects with low WHR was not different from that of controls. However, when looking at the magnitude of obesity in these patients, one can postulate that there was also some degree of abdominal fat deposit, which may pride the picture resulting from femoral deposits alone. Therefore, this study aimed at measuring insulin sensitivity in women with moderate lower-body obesity, compared to women with a similar degree of upper-body obesity and control women matched for age.

Materials and Methods

Subjects

We studied 20 lower-body overweight women (age 40.3 ± 2.3 years, WHR 0.75 ± 0.01, body mass index BMI 29.9 ± 0.7 kg/m^2, m ± SEM), 18 upper-body overweight women (age 40.4 ± 3 years, WHR 0.91 ± 0.02, BMI 29.4 ± 0.7 kg/m^2), and 28 control women matched for age and height (age 37.3 ± 1.8 years, WHR 0.7 ± 0.01, BMI 22.1 ± 0.3 kg/m^2), who participated as controls in previous metabolic studies. Subjects with impaired glucose tolerance according to the WHO criteria, subjects presenting signs suggestive for polycystic ovary syndrome or antecedents of gestational diabetes were excluded from the study. All patients were normotensive. Number of postmenopausal women (5 in the control group and 4 in each overweight group) was also matched. All postmenopausal women were treated with transcutaneous 17β-estradiol (0.050 mg per day) and oral progesterone (200 mg × 15 days). Informed consent was obtained from all subjects, and the study was approved by the local Ethics Committee.

Intravenous glucose tolerance test (IVGTT) and minimal model analysis

Subjects were asked to fast for 12 h before the test which began at 09:00 a. m. A cannula was set in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while

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glucose injection was performed in the contralateral cephalic vein. Glucose (30%, 0.5 g/kg) was slowly injected during 3 min. Insulin (0.02 units/kg body weight i.e. 1 or 2 units) was injected intravenously immediately after time 19. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min following the onset of the glucose injection. Times 1 and 3 were used for the determination of insulin early secretory phase [4]. The other times were necessary for minimal model calculations [5]. Analysis of IVGTT according to Bergman's minimal model of glucose disposal [6] was performed with the software "TISPAG" from our Department, which gave the values of insulin sensitivity SI and glucose effectiveness Sg. Sg was divided into its two components: the contribution of hyperglycemia *per se* to tissue glucose utilisation and the effect of basal insulin on glucose uptake. The basal insulin component of Sg is termed basal insulin effect (BIE) and can be calculated as the product of basal insulin Ib and SI. Thus the contribution of non-insulin dependent glucose uptake (glucose effectiveness at zero insulin, GEZI) to glucose uptake is the difference between total Sg and the BIE. The validity of our procedure has been previously described [5] and the fractional standard deviations FSD were calculated for the accuracy of minimal model indices.

Laboratory measurements

Samples were analysed for plasma insulin by radioimmunoassay (kit INSIK-5 from Sorin Biomedica, Italy) and plasma glucose with a Beckman glucose analyser. Within-assay coefficient of variation CV for insulin was between 8.6% (low values) and 9.7% (high values). Between-assay CV for insulin was between 12.5% (low values) and 14.4% (high values). The sensitivity was 2 μU/ml.

Statistical analysis

Results are presented as mean ± SEM. Comparisons between groups were performed by the Kruskall-Wallis non parametric analysis of variance, followed, when significant differences were found, by the Mann-Whitney test. Level of significance was set at $p < 0.05$.

Results

The mean fractional standard deviations FSD for SI was 9 ± 0.7% and 10.2 ± 0.8% for Sg, which shows the precision of minimal model fitting. Results are presented in Table **1**. SI was significantly higher in lower-body obesity compared to upper-body obesity ($p < 0.001$) and controls ($p < 0.02$). The three groups had the same Sg. Sg was divided into its two components BIE and GEZI. While GEZI was not different among the three groups, BIE was significantly higher in lower-body overweight women than upper-body overweight women ($p < 0.01$) and controls ($p < 0.02$), and was lower in upper body overweight than controls ($p < 0.05$).

Discussion

This study reports that in women with moderate lower body obesity, insulin sensitivity, as estimated by the minimal model analysis of an intravenous glucose tolerance test, was better than in non-obese, age-matched women, whereas upper-body obesity was associated with marked insulin resistance.

Table 1 Parameters obtained from the IVGTT in patients and controls (mean ± SEM) $^{*}p < 0.05$ vs. controls $^{**}p < 0.02$ vs. controls $^{***}p < 0.001$ vs. controls

Groups	Lower-body obesity (n = 20)	Upper-body obesity (n = 18)	Controls (n = 28)
Ib (μU/ml)	8 ± 0.8	11.6 ± 1.3***	7.2 ± 0.3
I1 + 3 (μU/ml)	85.8 ± 10.2	93.9 ± 8.2	73.8 ± 7.1
SI ($min^{-1}/[\mu U/ml] \times 10^{-4}$)	11.2 ± 0.2**	2.6 ± 0.4***	6.1 ± 0.7
Sg ($min^{-1} \times 10^{-2}$)	2.6 ± 2.2	2.4 ± 0.1	2.7 ± 0.2
BIE ($min^{-1} \times 10^{-2}$)	0.8 ± 0.2**	0.3 ± 0.05*	0.5 ± 0.07
GEZI ($min^{-1} \times 10^{-2}$)	1.8 ± 0.3	2.1 ± 0.4	2.2 ± 0.2

Ib = basal insulinemia, I1 + 3 = sum of insulinemia at 1 and 3 min after glucose injection, SI = insulin sensitivity, Sg = glucose effectiveness, BIE = basal insulin effect, GEZI = glucose effectiveness at zero insulin.

On these grounds, we postulate that lower-body moderate obesity may be a favorable metabolic situation which, if these results are confirmed, would change the clinical attitude towards overweight.

The mechanism explaining the high value of SI in lower-body obesity remains to be clarified. However, by comparison with a proposed mechanism involved in the "Syndrome X", we can hypothesize that this kind of overweight, when it is associated with a reduced volume of intra-abdominal fat, results in lower circulating levels of free fatty acids (FFAs) in the portal circulation. Thus, it could reduce the FFA-induced inhibition of insulin action by the Randle effect. Consistent with this hypothesis, a higher FFA release from adipose tissue in upper- vs. lower-body obesity has been demonstrated [7]. Nevertheless, this hypothesis has to be confirmed with a more specific assessment of body composition than WHR, which cannot distinguish between intra-abdominal and subcutaneous fat.

Sex hormone status may also play a role in modifications of glucose disposal in various types of obesity. A physiological decrease in SI during the luteal phase of the menstrual cycle has been described [8]. Since in our study, IVGTT was randomly scheduled during the menstrual cycle, the effects of the cycle on SI are probably included in the variance of our results, but are not likely to induce a bias. On the other hand, menopause and its hormonal treatment as well as contraceptive pills have been taken into account in the matching of our groups and their influence on SI cannot explain our results.

Concerning Sg, which is an important component of glucose disposal [9], it is interesting to note that it was not different among the three groups. Its component BIE, which reflects insulin sensitivity, exhibited the same pattern than SI but the other component GEZI was quite the same in the three groups.

Conclusion

In this study, women with lower-body fat deposits appear to have a high value of insulin sensitivity which contrasts with the well-known impairment of SI in upper-body obesity. Such a difference in insulin sensitivity may explain some of the previously reported discrepancies between these two anatomical subtypes of obesity in terms of blood lipids, vascular risk, and

risk of diabetes. This confirms that body fat distribution could be more important than obesity in the pathogenesis of insulin resistance [10]. This finding may have practical applications for the management of lower-body obesity, which is mostly a cosmetic complaint and does not appear to be a risk factor like upper-body obesity. On the other hand, it remains to be clarified whether an increased SI has pathophysiological consequences, such as increased lipogenesis or a higher incidence of hypoglycemia.

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